Postgraduate Medical Journal (March 1976) **52**, 156–158.

5-Hydroxytryptamine (5-HT) in the whole-blood of patients with depressive illness

A. COPPEN *
M.D., F.R.C.Psych.

P. TURNER
B.Sc., M.D., F.R.C.P.

A. R. ROWSELL
M.B., B.S., F.R.C.S.

CHERYL PADGHAM
M.Sc.

* *Medical Research Council Neuropsychiatry Laboratory, West Park Hospital, Epsom, Surrey, and Department of Clinical Pharmacology, St Bartholomew's Hospital, London E.C.2.*

Summary

Whole-blood 5-HT was examined in thirty-five depressive patients not on antidepressants, and in comparable control subjects. The concentration of whole-blood 5-HT was significantly lower during depression, but returned to normal after clinical recovery.

Introduction

Many, but not all, investigations point to a decrease in 5-hydroxytryptamine (5-HT) synthesis in depressive illness (Coppen, 1972; Lapin and Oxenkrug, 1969). Thus, the concentration of brain 5-hydroxyindole acetic acid (5-HIAA) has been reported decreased in the brains of depressive suicides (Shaw, Camps and Eccleston, 1967; Bourne *et al.*, 1966; Pare *et al.*, 1969). The concentration of 5-HIAA in lumbar cerebrospinal fluid in depressive patients has been reported decreased both before and after the administration of probenecid (Coppen *et al.*, 1972; Ashcroft *et al.*, 1966; Van Praag, Korf and Puite, 1970; Sjöström, 1974).

The value of many of these investigations is limited by the difficulties in providing well controlled experiments because of the obvious difficulties in obtaining a random sample of healthy subjects of comparable age and sex for either the post-mortem studies or the cerebrospinal fluid studies. More recently the authors have been examining the concentration of free plasma-tryptophan which is an important factor in determining the concentration of brain tryptophan (Tagliamonte, Biggio and Gessa, 1971). The concentration of brain tryptophan is an important factor in determining the rate of brain 5-HT synthesis as the enzyme tryptophan hydroxylase is not normally saturated in the mammalian brain (Tagliamonte *et al.*, 1973; Fernstrom and Wurtman, 1971). In an initial investigation (Coppen, Eccleston and Peet, 1973) free plasma-tryptophan was found to be significantly decreased in female depressive patients, although this returned towards normal after clinical recovery. These findings have been confirmed (unpublished) in a further group of female depressives, and the findings have also been independently confirmed by Aylward (1973), who also reported a correlation between free plasma-tryptophan concentration and clinical improvement. If there is a decrease in free plasma-tryptophan, other organs than the brain synthesizing 5-HT should show a decreased synthesis of this compound; 5-HT is produced in many other organs, including the gut, kidney, liver, lungs. Most 5-HT that reaches the blood stream is transported by the blood platelets, and little 5-HT is detectable in the blood outside the platelets. Whole-blood estimates of blood 5-HT are essentially measures of platelet 5-HT.

A study of whole blood 5-HT was undertaken to see if any change in whole body 5-HT synthesis rates would be reflected in a change in blood 5-HT of patients suffering from a depressive illness.

Methods

Patients were suffering from a primary depressive illness severe enough to warrant admission to the Medical Research Council Neuropsychiatry Ward. No patient had a history of mania although many had had previous attacks of depression. Twenty-eight female patients and seven male depressives were studied. Details are shown in Tables 1 and 2. Most had not recently been treated with tricyclic or other antidepressants, or if they had, a drying-out period of at least 7 days was instituted, during which time they were also given a full ward diet. A certain number of patients was studied after clinical recovery, following electroconvulsive therapy, and a further group of patients was studied who were well and had been on lithium prophylaxis for periods of several months. Control subjects were psychiatrically normal volunteers of roughly comparable age.

Blood was collected from patients and controls at approximately 9 a.m. after overnight fasting. Whole-blood was heparinized and frozen and subsequently

TABLE 1. Whole blood 5-HT in female control subjects and patients before and after recovery from a depressive illness

		Age (years)		Whole blood 5-HT (ng/ml)	
	No.	mean	s.e.	mean	s.e.
Control subjects	27	44·3	1·8	171·2	9·6
Depressive patients	28	59·6	2·8	90·2	7·0
Recovered depressives	7	59·1	4·2	147·1	13·3
Recovered depressives (on lithium)	20	53·2	2·0	172·6	11·0

Controls *v.* depressive patients $t = 6{\cdot}85$, $P = < 0{\cdot}001$
Depressive patients *v.* recovered depressives $t = 3{\cdot}65$, $P = < 0{\cdot}001$.

TABLE 2. Whole blood 5-HT in male control subjects and patients before and after recovery from a depressive illness

		Age (years)		Whole blood 5-HT (ng/ml)	
Group	No.	mean	s.e.	mean	s.e.
Control subjects	31	48·9	2·2	131·2	8·9
Depressive patients	7	51·4	2·5	74·1	10·6
Recovered depressives (on lithium)	10	50·9	3·0	180·6	14·1

Controls *v.* depressive patients $t = 2{\cdot}92$, $P = < 0{\cdot}01$
Controls *v.* recovered depressives (on lithium) $t = 2{\cdot}79$, $P = < 0{\cdot}01$
Depressive *v.* recovered depressives (on lithium) $t = 5{\cdot}56$, $P = < 0{\cdot}001$.

measured by the fluorometric method of Ashcroft *et al.* (1964). The lower limit of resolution was 40 ng/ml.

Results

These are shown in Table 1 and Table 2. No correlation was found between blood 5-HT and age in either controls or depressive subjects, but an interesting difference was found in that the male controls had lower whole blood 5-HT than the female controls. The age of the controls and patients were comparable.

Both male and female patients showed comparable results. Patients when depressed showed a very significant decrease in whole blood 5-HT. After clinical recovery patients' whole-blood 5-HT returned to normal whether untreated or on lithium. The male patients on lithium had higher levels than the male controls.

Discussion

The blood platelets rapidly take up recently synthesized 5-HT that enters the blood stream and these results may be related to the lowering of free plasma-tryptophan that has recently been reported (Coppen *et al.*, 1973), as this may limit the production of 5-HT in various organs of the body. The finding, in the males at least, that lithium-treated patients have increased blood 5-HT is in keeping with the observations of Murphy *et al.* (1970) that lithium stimulated amine transport into platelets. A reduced uptake of 5-HT into the platelets of patients with endogenous depression has been described by Hallstrom *et al.* (1975), but this was not found by other workers (Shaw *et al.*, 1971).

The results are also in keeping with earlier findings of a decreased urinary excretion of tryptamine in a carefully controlled study on depressed patients (Coppen *et al.*, 1965). The urinary excretion of tryptamine, which probably results from tryptophan metabolism in the kidney was approximately half that of normal during a depressive illness. This also could be accounted for by a decrease in free plasma-tryptophan reducing the amount of tryptophan available for metabolism by the kidney.

The findings, therefore, tend to support the notion that there is a general decrease of 5-HT synthesis in depressive patients and this may be the result of a lowered free plasma-tryptophan. The aetiological importance of these results for depressive illness remains to be elucidated although the association between free plasma-tryptophan and the REM phase of sleep that we recently reported indicates that free plasma-tryptophan may have important functional effects on the central nervous system of man (Chen *et al.*, 1974).

Acknowledgments

We are indebted to J. Bailey for the statistical evaluation of the data.

A. R. Rowsell was in receipt of a grant from the Migraine Trust.

References

ASHCROFT, G.W., CRAWFORD, T.B.B., BINNS, J.K. & MACDOUGALL, E.J. (1964) Estimation of 5-hydroxytryptamine in human blood. *Clinica chimica acta*, **9**, 364.

ASHCROFT, G.W., CRAWFORD, T.B.B., ECCLESTON, D., SHARMAN, D.F., MACDOUGALL, E.J., STANTON, J.B. & BINNS, J.F. (1966) 5-Hydroxyindole compounds in the cerebrospinal fluid of patients with psychiatric or neurological diseases. *Lancet*, **ii**, 1049.

AYLWARD, M. (1973) Plasma tryptophan levels and mental depression in post-menopausal subjects: effects of oral piperazine-oestrone sulphate. *International Research Communications System*,

BOURNE, H.R., BUNNEY, W.E., COLBURN, R.W., DAVIES, J.O., DAVIS, J.M., SHAW, D.M. & COPPEN, A. (1966) Noradrenaline, 5-hydroxytryptamine and 5-hydroxyindoleacetic acid in hindbrains of suicidal patients. *Lancet*, **ii**, 805.

CHEN, C.N., KALUCY, R.S., HARTMAN, M.K., LACEY, J.H., CRISP, A.H., BAILEY, J., ECCLESTON, E.G. & COPPEN, A. (1974) Plasma tryptophan and sleep. *British Medical Journal*, **4**, 564.

COPPEN, A. (1972) Serotonin in the affective disorders. *Journal of Psychiatric Research*, **9**, 163.

COPPEN, A., ECCLESTON, E. & PEET, M. (1973) Total and free tryptophan in the plasma of depressive patients. *Lancet*, **ii**, 60.

COPPEN, A., PRANGE, A., WHYBROW, P. & NOGUERA, R. (1972) Abnormalities of indoleamines in affective disorders. *Archives of General Psychiatry*, **26**, 474.

COPPEN, A., SHAW, D.M., MALLESON, A., ECCLESTON, E. & GUNDY, G. (1965) Tryptamine metabolism in depression. *British Journal of Psychiatry*, **111**, 993.

FERNSTROM, J.D. & WURTMAN, R.J. (1971) Brain serotonin content: physiological dependance on plasma tryptophan levels. *Science*, **173**, 149.

HALLSTROM, C.O.S., REES, W.L., PARE, C.M.B., TRENCHARD, A. & TURNER, P. (1976) Platelet uptake of 5-hydroxytryptamine and dopamine in depression. *Postgraduate Medical Journal* (Suppl.), **52** (in press).

LAPIN, I.P. & OXENKRUG, G.F. (1969) Intensification of the central serotonergic processes as a possible determinant of the thymoleptic effect. *Lancet*, **i**, 132.

MURPHY, D.L., COLBURN, R.W., DAVIS, J.M. & BUNNEY, W.E. (1970) Imipramine and lithium effects on biogenic amine transport in depressive patients. *American Journal of Psychiatry*, **127**, 115.

PARE, C.M.B., YEUNG, D.P.H., PRICE, K. & STACEY, R.S. (1969) 5-Hydroxytryptamine, noradrenaline and dopamine in brain stem, hypothalamus and caudate nucleus of controls and patients committing suicide by coal gas poisoning. *Lancet*, **ii**, 133.

SHAW, D.M., CAMPS, F.E. & ECCLESTON, E.G. (1967) 5-Hydroxytryptamine in the hindbrain of depressive suicides. *British Journal of Psychiatry*, **113**, 1407.

SHAW, D., SWEENEY, D.A., WOODCOCK, N. & BEVAN-JONES, A. (1971) Uptake and release of ^{14}C-5-hydroxytryptamine by platelets in affective illness. *Journal of Neurology, Neurosurgery and Psychiatry*, **34**, 224.

SJÖSTRÖM, R. (1974) Diagnosis of manic-depressive psychosis from cerebrospinal concentration of 5-hydroxyindoleacetic acid. *Advances in Biochemical Psychopharmacology*, **11**, 369.

TAGLIAMONTE, A., BIGGIO, G. & GESSA, G.L. (1971) Possible role of 'free' plasma tryptophan in controlling brain tryptophan concentrations. *Rivista di Farmacologia e Terapia*, **2**, 251.

TAGLIAMONTE, A., BIGGIO, G., VARGIU, L. & GESSA, G.L. (1973) Free tryptophan in serum controls, brain tryptophan level and serotonin synthesis. *Life Sciences*, **12**, 277.

VAN PRAAG, H.M., KORF, J. & PUITE, J. (1970) 5-Hydroxyindoleacetic acid levels in the cerebrospinal fluid of depressive patients treated with probenecid. *Nature*, London, **225**, 1259.